

# MSKCC and DFCI Debate Current Treatment Strategies in Multiple Myeloma



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In part 2 of a recent *Face Off* event hosted by CancerNetwork®, the Memorial Sloan Kettering Cancer Center (MSKCC) “Yankees” were again up against the Dana-Farber Cancer Institute (DFCI) “Red Sox,” this time to discuss treatments in multiple myeloma. The MSKCC team was led by **Malin Hultcrantz, MD, PhD**, and **Carlyn Rose Tan, MD**, both assistant attending physicians at the cancer center. The DFCI team was led by **Omar Nadeem, MD**, clinical director of both the Myeloma Immune Effector Cell Therapy Program and the Center for Prevention of Progression and associate director of the Multiple Myeloma Clinical Research Program at DFCI as well as instructor in medicine at Harvard Medical School; and **Clifton C. Mo, MD**, director of autologous stem cell transplantation for multiple myeloma and associate director of the Multiple Myeloma Clinical Research Program at DFCI as well as assistant professor of medicine at Harvard Medical School.

The panelists discussed and debated current preferred treatments for multiple myeloma. Each team was given the chance to defend their choices, and a live audience voted on each presentation to determine a winner.

## Review of DETERMINATION and GRIFFIN

### DETERMINATION

The phase 3 DETERMINATION trial (NCT01208662) analyzed the triplet regimen of lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVd) with or without autologous stem cell transplant (ASCT) in patients with newly diagnosed multiple myeloma.<sup>1</sup> Patients were randomly assigned 1:1 to the RVd-alone group (n = 357) or the ASCT group (n = 365). All patients received 1 cycle of RVd before randomization and 2 cycles after randomization, followed by stem cell collection. Five additional cycles of RVd were given to those in the nontransplant group, and

the transplant group received 200 mg of melphalan, ASCT, and 2 additional cycles of RVd. Maintenance therapy in both groups included daily lenalidomide with 10 mg on the first day, and 15 mg thereafter.

Patients had a median duration of treatment of 28.2 months (95% CI, 21.1-36.3) in the RVd group and 36.1 months (95% CI, 28.5-41.5) in the ASCT group; the median duration of maintenance therapy was 36.4 months (95% CI, 25.7-40.8) and 41.5 months (95% CI, 34.0-47.1), respectively. Of note, 310 patients (84.9%) in the transplant group underwent ASCT.

At a median follow-up of 76.0 months, the median progression-free survival (PFS) in the RVd group was 46.2 months (95% CI, 38.1-53.7) vs 67.5 months (95% CI, 58.6-not reached) in the ASCT group. In patients who had high-risk cytogenetics, the median PFS was 17.1 months in the RVd group and 55.5 months in the ASCT group. Patients had a median duration of response of 38.9 months in the RVd group and 56.4 months in the ASCT group (HR, 1.45; 95% CI, 1.09-1.93). At 5 years, 52.9% of patients in the RVd group had a complete response or better vs 60.6% in the ASCT group.

In patients with no detectable minimal residual disease (MRD) at the start of lenalidomide maintenance, the 5-year PFS rate was 59.2% vs 53.5% in the RVd and ASCT groups, respectively (HR, 0.91; 95% CI, 0.46-1.79). In those with detectable MRD, the median PFS was 33.3 months vs 50.6 months in the RVd and ASCT groups, respectively (HR, 1.67; 95% CI, 0.98-2.85).

The estimated 5-year overall survival (OS) rates were 79.2% vs 80.7% in the RVd and ASCT groups, respectively (HR, 1.10; 95% CI, 0.73-1.65;  $P > .99$ ). For those with high cytogenetic risk,

the corresponding rates were 54.3% vs 63.4%.

Treatment-related adverse effects (TRAEs) that were grade 3 or higher occurred in 78.2% of patients in the RVd group vs 94.2% in the ASCT group; 60.5% vs 89.8%, respectively, reported hematologic TRAEs of grade 3 or higher ( $P < .001$ ). Serious AEs related to treatment occurred in 40.3% in the RVd group and 47.1% in the ASCT group, with serious treatment-related infections were reported in 11.3% vs 16.6%, respectively.

### GRIFFIN

The phase 2 GRIFFIN study (NCT02874742) analyzed daratumumab (Darzalex) plus RVd induction and consolidation treatment plus daratumumab/lenalidomide maintenance therapy (D-RVd/D-R) vs RVd alone in patients with transplant-eligible, newly diagnosed multiple myeloma.<sup>2</sup> Patients in the investigative arm received induction D-RVd for 4 cycles, consolidation D-RVd for 2 additional cycles, and maintenance D-R until disease progression or for up to 2 years. The control group received

matched RVd for induction and consolidation and lenalidomide alone for maintenance therapy.

At the final analysis, the median follow-up was 49.6 months with a clinically meaningful reduction in the risk of disease progression or death of 55% in the D-RVd/D-R arm vs the RVd arm (HR, 0.45; 95% CI, 0.21-0.95;  $P = .0324$ ). At the time of data presentation, the median PFS had not been reached for either arm, with separation in the curves occurring beyond 1 year of maintenance therapy. In the D-RVd arm, 14% of patients who had MRD-positive status at the end of consolidation converted to MRD-negative status at the end of the 2-year maintenance period; the comparable figure was 10% in the RVd group.

The most common grade 3/4 hematologic treatment-emergent AEs (TEAEs) included neutropenia (46% vs 23%), thrombocytopenia (16% vs 9%), leukopenia (17% vs 8%), and lymphopenia (23% vs 23%) in the D-RVd and RVd arms, respectively. Grade 3/4 nonhematologic TEAEs included fatigue (7% vs 6%), upper respiratory tract infection (4% vs 2%), diarrhea (7% vs 5%), and peripheral neuropathy (7% vs 9%).

## Yankees With Bases Loaded: DFCI Questions MSKCC on Key Presentation Points

**NADEEM:** How do you determine if a transplant is the optimal course of treatment for patients with multiple myeloma?

**TAN:** We need to wait for the median OS [data] to mature. I have a discussion with the patient, ultimately, about the risks and benefits and what their preference might be. If they [have] high-risk cytogenetics, I [am] pushier in terms of doing an up front transplant. The median PFS [in patients with high-risk cytogenetics on DETERMINATION] was 17 months vs 55 months for RVd alone vs RVd/ASCT. Part of it is also their age. If they're 72 years old, you

want to get [them to transplant] sooner rather than later in terms of tolerability.

**NADEEM:** The GRIFFIN trial used maintenance therapy. What are your thoughts on patients who receive maintenance therapy with a quadruplet induction?

**TAN:** When you look at the GRIFFIN trial, the response rates and the MRD negativity rates between the first year and the second year, while the [patients] are on maintenance, don't necessarily deepen any further. In the trial, a stringent complete response rate of 60% was observed. I'm not sure how much more

benefit they might be deriving at [the time of maintenance].

**MO:** When looking at the median follow-up between the DETERMINATION and GRIFFIN studies, how much longer do we need to wait [after treatment] before we can reasonably say patients don't need to receive intensive therapy up front?

**TAN:** For patients with high-risk disease, I would encourage them to proceed with upfront transplant but I'm not necessarily that pushy with patients if they have standard-risk cytogenetics.

## Presentation of the INSURE and ICARIA-MM Trials

### INSURE

The INSURE study is a pooled analysis of patients with relapsed/refractory multiple myeloma who have received ixazomib (Ninlaro), lenalidomide, and dexamethasone (IRd) as a second or later line of therapy.<sup>3</sup> The studies included in the pooled analysis were INSIGHT MM (NCT02761187), UVEA-IXA, and REMIX, with a total of 564 patients.<sup>4-6</sup>

The median time to next treatment was 18.4 months (95% CI, 15.3-20.8), but it was longer in those who received ixazomib as second-line therapy at 20.7 months (95% CI, 17.0-27.5). The median PFS in the overall population was 19.9 months (95% CI, 16.6-23.6), and it was 21.7 months (95% CI, 18.6-35.2) in those receiving ixazomib in the second line. Overall, the median time to best response was 4.0 months, and the overall

response rate (ORR) was 65%. In those who received ixazomib in the second line, the median time to best response was 3.9 months and the ORR was 70%. When looking at patients by frailty status, the median time to best response was 4.7 months with an ORR of 67% in the nonfrail group vs 3.2 months and 59%, respectively, in the frail group.

### ICARIA-MM

The phase 3 ICARIA-MM trial (NCT02990338) investigated isatuximab (Sarclisa) plus pomalidomide (Pomalyst) and low-dose dexamethasone vs pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma.<sup>7</sup> A total of 307 patients were randomly assigned to either the isatuximab (n = 154) or the control group (n = 153).

The median duration of treatment was

47.6 weeks in the isatuximab group and 24.0 weeks in the control group with a median follow-up duration of 35.3 months. The median PFS was 11.1 months (95% CI, 7.8-13.8) in the isatuximab group vs 5.9 months (95% CI, 4.5-7.9) in the control group (HR, 0.60; 95% CI, 0.46-0.78;  $P < .0001$ ). The median OS in the isatuximab group was 24.6 months (95% CI, 20.3-31.3) vs 17.7 months (95% CI, 14.4-26.2) in the control group (HR, 0.76; 95% CI, 0.57-1.01;  $P = .028$ ). MRD negativity was observed in 7% of patients at the  $10^{-5}$  sensitivity level in the isatuximab group vs none in the control group.

Serious TEAEs occurred in 73% of patients in the isatuximab group vs 60% in the control group. The most commonly occurring serious AE was pneumonia in 23% vs 21% of the isatuximab and control groups, respectively.

## Red Sox Base Hit: MSKCC Challenges DFCI Key Data Points

**HULTCRANTZ:** How would you best use isatuximab/lenalidomide or ixazomib/lenalidomide for patients with multiple myeloma?

**MO:** The combination of ixazomib/lenalidomide won't be ideal for most patients because most will be lenalidomide refractory by the time they reach the second line of therapy. The more interesting question is about the role of ixazomib in combination with other drugs, specifically pomalidomide. We have some data on that now. The initial results of a phase 1/2 study of twice-weekly ixazomib with pomalidomide and dexamethasone were reported at the 2021 American Society of Hematology Annual Meeting.<sup>8</sup> Things are looking promising. I do think there's a role for this drug. Oral availability should

not be undervalued. I relied heavily on ixazomib for a number of patients in 2020 and still have many patients who switched from bortezomib to ixazomib and have not gone back because they're doing quite well. Especially in myeloma, at least for now, we're still asking our patients to be treated for a long time. In DETERMINATION, with lenalidomide maintenance, there's real value, at least to some patients, to not having to wait in the infusion chair once or twice a month for years on end. The oral availability is important.

**HULTCRANTZ:** What are your thoughts on isatuximab?

**MO:** When you look at the comparator arms of ICARIA/APOLLO [NCT03180736] vs CANDOR [NCT03158688] / IKEMA [NCT0327528], it's hard to ignore how

well people are doing in the carfilzomib/dexamethasone doublet vs the pomalidomide/dexamethasone doublet comparator arms in a similar patient population.<sup>9-11</sup> The carfilzomib-based monoclonal antibody triplets are the most efficacious, comparing across studies—which we're not supposed to do, and yet always do. We have a predominantly older, 60s-plus patient population, a significant percentage of whom have either known cardiac disease or multiple risk factors for cardiac events. For patients in whom you're worried about the cardiotoxicity of carfilzomib, the isatuximab/pomalidomide/dexamethasone triplet is especially attractive.

The event ended in a "homerun" for the MSKCC Yankees, who won the *Face Off* against the DFCI Red Sox with 24 points points after both teams showcased their knowledge and expertise in their respective fields. ■

 For references visit [cancernetwork.com/face-off\\_12.22](https://cancernetwork.com/face-off_12.22)